10-28-2021

Disease Control After Hypofractionation Versus Conventional Fractionation for Triple Negative Breast Cancer: Comparative Effectiveness in a Large Observational Cohort

Reshma Jagsi

Kent A. Griffith

Frank A. Vicini

Eyad Abu-Isa

Derek Bergsma

See next page for additional authors

Recommended Citation

Jagsi R, Griffith KA, Vicini FA, Abu-Isa E, Bergsma D, Bhatt A, Dilworth JT, Dominello M, Franklin S, Heimburger DK, Kaufman I, Kocheril PG, Kretzler AE, Paximadis P, Radawski JD, Walker EM, and Pierce L. Disease Control After Hypofractionation Versus Conventional Fractionation for Triple Negative Breast Cancer: Comparative Effectiveness in a Large Observational Cohort. Int J Radiat Oncol Biol Phys 2021.

Authors

Reshma Jagsi, Kent A. Griffith, Frank A. Vicini, Eyad Abu-Isa, Derek Bergsma, Amit Bhatt, Joshua T. Dilworth, Michael Dominello, Stephen Franklin, David K. Heimburger, Isaac Kaufman, Paul G. Kocheril, Annette E. Kretzler, Peter Paximadis, Jeffrey D. Radawski, Eleanor M. Walker, and Lori Pierce

INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
www.redjournal.org

Clinical Investigation

Disease Control After Hypofractionation Versus Conventional Fractionation for Triple Negative Breast Cancer: Comparative Effectiveness in a Large Observational Cohort

Reshma Jagsi, MD, DPhil,[a] Kent A. Griffith, MS, MPH,[b] Frank A. Vicini, MD,[c] Eyad Abu-Isa, MD,[a,d] Derek Bergsma, MD,[a,e] Amit Bhatt, MD, PhD,[f] Joshua T. Dilworth, MD, PhD,[g] Michael Dominello, DO,[h,i] Stephen Franklin, MD,[j] David K. Heimburger, MD,[k] Isaac Kaufman, MD,[l] Paul G. Kocheril, MD,[m] Annette E. Kretzler, MD,[n] Peter Paximadis, MD,[o] Jeffrey D. Radawski, MD,[p] Eleanor M. Walker, MD,[n] and Lori Pierce, MD[a] on behalf of the Michigan Radiation Oncology Quality Consortium

[a]Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan; [b]Department of Biostatistics, University of Michigan, Ann Arbor, Michigan; [c]21st Century Oncology, Michigan Healthcare Professionals, Farmington Hills, Michigan; [d]Ascension Providence Hospital, Southfield, Michigan; [e]Mercy Health Radiation Oncology, Grand Rapids, Michigan; [f]Karmanos Cancer Institute at McLaren Greater Lansing, Lansing, Michigan; [g]Beaumont Radiation Oncology, Royal Oak, Michigan; [h]Department of Radiation Oncology, Wayne State University, Detroit, Michigan; [i]Karmanos Cancer Center, Detroit, Michigan; [j]Karmanos Cancer Institute at McLaren Macomb, Ted B. Wahby Cancer Center, Mount Clemens, Michigan; [k]Munson Medical Center, Traverse City, Michigan; [l]Karmanos Cancer Institute at McLaren Northern, Petosky, Michigan; [m]Genesys Hurley Cancer Institute, Flint, Michigan; [n]Department of Radiation Oncology, Henry Ford Health System, Jackson, Michigan; [o]Lakeland Radiation Oncology, St. Joseph, Michigan; and [p]West Michigan Cancer Center, Kalamazoo, Michigan

Received Sep 10, 2021; Revised Oct 11, 2021; Accepted for publication Oct 15, 2021

Purpose: Questions remain about whether moderately hypofractionated whole-breast irradiation is appropriate for patients with triple-negative breast cancer.

Methods and Materials: Using the prospective database of a multicenter, collaborative quality improvement consortium, we identified patients with node-negative, triple-negative breast cancer who received whole-breast irradiation with either moderate hypofractionation or conventional fractionation. Using inverse probability of treatment weighting (IPTW), we compared

Corresponding author; E-mail: rjagsi@med.umich.edu

This study has been supported by a Michigan Medicine Rogel Cancer Center Discovery Award and the Komen Foundation. Blue Cross Blue Shield of Michigan supports the Michigan Radiation Oncology Quality Consortium through payments to the institutions of all authors. None of these had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Acknowledgments—The authors gratefully acknowledge the extensive support that made this work possible, including the assistance of Lauren Szczygiel, Chris Krenz, Rhonda Hubbard, and Melissa Mietzel at the University of Michigan and the contributions of the staff and patients at the centers that contributed data.

Disclosures: R.J. has stock options as compensation for her advisory board role in Equity Quotient; has received personal fees from the Greenwall Foundation, the Doris Duke Foundation, and the National Institutes of Health; has received grants or contracts for unrelated work from the National Institutes of Health, the Doris Duke Foundation, the Greenwall Foundation, the Komen Foundation, Genentech, and Blue Cross Blue Shield of Michigan for the Michigan Radiation Oncology Quality Consortium; and has served as an expert witness for Sherinian and Hasso, Dressman Benzinger LaVelle, and Kleinbard, LLC. P.G.K. reports receiving an honorarium for the Congdon lecture series from Ascension Genesys Hospital. E.M.W. reports receiving grants or contracts for unrelated work from Pfizer and Genentech. L.P. reports patents associated with PFS Genomics, a subsidiary of Exact Sciences, and has leadership or fiduciary roles with the American Society of Clinical Oncology and the BCRF Advisory Board.

Research data are the property of the individual sites and cannot be shared.

Int J Radiation Oncol Biol Phys, Vol. 000, No. 00, pp. 1–8, 2021
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2021.10.012

outcomes using the Kaplan-Meier product-limit estimation method with Cox regression models estimating the hazard ratio for time-to-event endpoints between groups.

Results: The sample included 538 patients treated at 18 centers in 1 state in the United States, of whom 307 received conventionally fractionated whole-breast irradiation and 231 received moderately hypofractionated whole-breast irradiation. The median follow-up time was 5.0 years (95% confidence interval [CI], 4.77-5.15 years). The 5-year IPTW estimates for freedom from local recurrence were 93.6% (95% CI, 87.8%-96.7%) in the moderate hypofractionation group and 94.4% (95% CI, 90.3%-96.8%) in the conventional fractionation group. The hazard ratio was 1.05 (95% CI, 0.51-2.17; P = .89). The 5-year IPTW estimates for recurrence-free survival were 87.8% (95% CI, 81.0%-92.4%) in the moderate hypofractionation group and 88.4% (95% CI 83.2%-92.1%) in the conventional fractionation group. The hazard ratio was 1.02 (95% CI, 0.62-1.67; P = .95). The 5-year IPTW estimates for overall survival were 96.6% (95% CI, 92.0%-98.5%) in the moderate hypofractionation group and 93.4% (95% CI, 88.7%-96.1%) in the conventional fractionation group. The hazard ratio was 0.65 (95% CI, 0.30-1.42; P = .28).

Conclusions: Analysis of outcomes in this large observational cohort of patients with triple-negative, node-negative breast cancer treated with whole-breast irradiation revealed no differences by dose fractionation. This adds evidence to support the use of moderate hypofractionation in patients with triple-negative disease.

Introduction

Whole-breast moderate hypofractionation is a less costly and less burdensome approach to adjuvant radiation therapy for women with breast cancer, requiring only 3 weeks (15-16 fractions to 40-42.5 Gy), compared with conventional fractionation, which requires 5 weeks or longer (50-50.4 Gy in 25-28 fractions). Large randomized trials from Canada[1] and the United Kingdom[2] established the overall safety and efficacy of whole-breast moderate hypofractionation among patients with early-stage invasive breast cancer, leading clinical practice guidelines to embrace this as the preferred approach for whole-breast irradiation.[3]

Questions have lingered, however,[4] particularly regarding the appropriateness of moderate hypofractionation among patients with triple-negative disease. Breast and prostate cancers may generally have a lower alpha-beta ratio than the head and neck squamous cell carcinomas that were evaluated to derive an initial understanding of sensitivity to dose fractionation.[5] However, questions remain about whether the lower alpha-beta ratio is specific to hormone-sensitive subtypes, which constitute the majority of these cancers, and whether using a higher dose per fraction compared with a lower total dose as prescribed by modern schedules of moderate hypofractionation is also equally effective in triple-negative cancers. Existing data to address these questions are limited in that the large British trials did not collect subtype information. Therefore, the only evidence describing subtype-specific outcomes from randomized comparison to inform the most recent American Society for Radiation Oncology (ASTRO) guidelines used data from a subset of patients enrolled on a Canadian (Ontario Clinical Oncology Group [OCOG]) randomized trial.[6] In that analysis, breast cancer subtype (luminal A, luminal B, HER2 enriched, and basal) was measured using immunohistochemistry and fluorescence in situ hybridization. Risk of local recurrence did not differ significantly by treatment arm when stratified by molecular subtype, but the point estimates reported were in the direction of improved outcomes with hypofractionation for luminal A tumors (hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.24-1.33), whereas the point estimate was in the opposite direction for those with basal (triple-negative) disease (HR, 1.27; 95% CI, 0.21-7.58). Although this interaction was not statistically significant, the comprehensive ASTRO consensus guideline on whole-breast fractionation emphasized the limitations of existing evidence and importance of additional research in this area because of the low power to detect an interaction between subtype and treatment arm based on the size of the subgroups in the OCOG analysis, which included only 125 patients with basal tumors.[7]

Since the publication of the aforementioned guideline, informative data have emerged from 2 additional trials. Rates of local recurrence were similar after conventional fractionation and moderate hypofractionation in the subgroup of 77 patients with triple-negative disease in a randomized trial from China[8] and in a subgroup of 188 patients with triple-negative disease in a randomized trial from Denmark, Germany, and Norway.[9] In an editorial accompanying the publication of the trials, Abram Recht noted that these contributions help to advance understanding but maintained that "there is not yet sufficient evidence to confidently reach a verdict on many of the important questions outlined above [including whether moderate hypofractionation is equally effective in patients with triple-negative disease]. Ongoing and future trials and retrospective analyses of existing studies will need to focus on those questions."[10] One such study was recently led using a large prospective observational cohort from Canada, which included 603 patients with triple-negative cancer, finding no difference in local recurrence-free survival in those patients.[11] Using a similarly large observational cohort from the United States, we sought to collect additional evidence to address the gap in knowledge on this important question.

Methods and Materials

Sample design and data collection

We queried a prospective database of a statewide collaborative quality improvement consortium that enrolls all patients receiving whole-breast irradiation at participating facilities. We identified 672 patients with invasive, node-negative, triple-negative breast cancer treated between January 1, 2012, and December 31, 2018 (dates were selected to allow a median follow-up of approximately 5 years). Because the consortium does not follow patients for disease control, we initiated a voluntary research study with physician leads from 18 of the 23 centers with eligible cases, to gather disease control information.

Each of the 18 centers submitted applications to their institutional review boards and received approval to conduct this research study. Sites collected data using standardized forms with anonymous identifiers that allowed the newly collected information to be merged with the data already present in the consortium database, including radiation dose-fractionation, for centralized analysis.

The 18 centers included 573 of the 672 potential cases. We received data for 558 cases, with 13 of 18 centers returning data for all cases and with the lowest return rate being 81.82% from 2 institutions. Furthermore, we requeried the received cases and excluded any cases that were missing receptor status for ER, PR, or HER2/Neu, resulting in an exclusion of 14 additional cases. Six cases had no follow-up information, leaving 538 cases in the final analytical sample.

Outcomes measures

We considered 3 outcomes using time-to-event endpoints. First, we considered freedom from local recurrence (FFLR), with the time constructed from the date of lumpectomy until the date of local recurrence or censored on the date of mastectomy (for patients who elected later to have mastectomy unrelated to recurrence), death, or last known contact. Second, we considered recurrence-free survival (RFS), with the time constructed from the date of lumpectomy until the first of date of recurrence (any location) or date of death, or censored on the date of last known contact. Finally, we determined overall survival (OS), with the time constructed from the date of lumpectomy until the date of death or censored on the date of last known contact.

Analytical approach

The effects of moderately hypofractionated and conventionally fractionated regimens were compared for the 3 time-to-event endpoints using the Kaplan-Meier product-limit estimation method. Because fractionation treatment decisions were made based on provider preference and the patient's clinical characteristics, we expected some bias in treatment selection to be present in this observational sample. Comparisons in an unadjusted fashion for time-to-event endpoints would therefore be biased by any differences in predictive and prognostic characteristics between the treatment groups. We assessed the degree of difference in covariates between treatment groups using the standardized difference, finding that several covariates had absolute difference values of 10 or greater, suggesting significant imbalance between groups.[12] Therefore, we proceeded to implement a balancing technique, using propensity score creation for the treatment assignment and weighting subsequent analyses by the inverse probability of treatment assignment to correct these imbalances.

Propensity scores were calculated using multiple variable logistic regression with the following covariates: age groups (<50 years, 50 to <60 years, 60 to <70 years, and 70 years or older), race (White vs Black or other), body mass index (in kg/m^2) categories (<25, underweight/normal weight; 25 to <30, overweight; 30 to <35, obesity I; and ≥35, obesity II/III), comorbidity group (0, 1, 2, or 3 or more comorbidities), smoking status (never, former, or current), chemotherapy (yes or no), T stage (0/1 vs 2/3), tumor grade (1 [well]/2 [moderately] vs 3 [poorly differentiated]), surgical margins (close/positive vs negative), and breast volume, modeled using a restricted cubic spline with 5 knots spaced using the observed percentiles. The covariates for the propensity model were chosen using subject matter knowledge about appropriate predictive and prognostic characteristics, and categorization was modified so extremely small groups of patients were avoided: Black patients were grouped with patients of other races (a very small group), certain T stages were grouped together (0 with 1 and 2 with 3), and tumor grades were grouped (1 with 2). Propensity score calculation requires complete information for the chosen characteristics; otherwise, the propensity score is missing. Therefore, the amount of missingness needs to remain low (<3% of the total sample) for chosen covariates. Thus, a decision was made not to include lymphovascular invasion, which was collected with a higher degree of missingness (16.2%). Using the propensity model as described, propensity scores could be calculated for 520 of the 538 cases composing the analytical sample. Because the total amount of missingness for propensity scores was low, methods to impute the limited missing data were not necessary to implement.

Product-limit 5-year estimates for the time-to-event endpoints were created after inverse probability of treatment weighting (IPTW). Finally, Cox regression models were created to estimate the hazard ratio for time-to-event endpoints between groups. A sensitivity analysis restricted to cases that received boost radiation therapy was also conducted. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, North Carolina).

Results

Of the 538 cases in the analytical sample, 307 received conventionally fractionated whole-breast irradiation and 231 received moderately hypofractionated whole-breast irradiation. A large

Table 1 Key Patient, Treatment, and Tumor Characteristics

		Unweighted sample description				Propensity (IPTW[‡]) weighted sample description			
Variable/Level	Summary	ALL	CWBI	AWBI	D[†]	ALL	CWBI	AWBI	D[†]
Age group: Age < 50	N (%)	82 (15.24)	66 (21.50)	16 (6.93)	-42.672	82 (15.96)	46 (15.75)	36 (16.23)	1.330
Age group: 50 <= Age < 60	N (%)	146 (27.14)	90 (29.32)	56 (24.24)	-11.476	148 (28.50)	85 (28.86)	63 (28.03)	-1.844
Age group 60 <= Age < 70	N (%)	163 (30.30)	101 (32.90)	62 (26.84)	-13.268	153 (29.47)	88 (30.04)	64 (28.73)	-2.866
Age group: 70 <= Age	N (%)	147 (27.32)	50 (16.29)	97 (41.99)	58.976	135 (26.07)	74 (25.35)	60 (27.00)	3.754
Race: 1 = White	N (%)	333 (61.90)	173 (56.35)	160 (69.26)	26.958	313 (60.20)	178 (60.44)	134 (59.88)	-1.137
Race: 2 = Black	N (%)	177 (32.90)	113 (36.81)	64 (27.71)	-19.565	176 (33.96)	98 (33.41)	78 (34.69)	2.685
Race: 3 = Other	N (%)	28 (5.20)	21 (6.84)	7 (3.03)	-17.658	30 (5.84)	18 (6.15)	12 (5.43)	-3.063
Comorbidity group: 0	N (%)	200 (37.17)	119 (38.76)	81 (35.06)	-7.667	198 (38.16)	110 (37.59)	87 (38.91)	2.711
Comorbidity group: 1	N (%)	185 (34.39)	105 (34.20)	80 (34.63)	0.905	172 (33.08)	97 (33.19)	74 (32.95)	-0.511
Comorbidity group: 2	N (%)	99 (18.40)	52 (16.94)	47 (20.35)	8.760	97 (18.76)	56 (19.09)	41 (18.33)	-1.955
Comorbidity group: 3+	N (%)	54 (10.04)	31 (10.10)	23 (9.96)	-0.469	51 (9.99)	29 (10.13)	22 (9.81)	-1.049
Smoking Status: Missing	N (%)	3 (0.56)	2 (0.65)	1 (0.43)	-2.977				.
Smoking Status: Never	N (%)	295 (54.83)	172 (56.03)	123 (53.25)	-5.585	290 (55.92)	163 (55.42)	127 (56.58)	2.341
Smoking Status: Former	N (%)	175 (32.53)	96 (31.27)	79 (34.20)	6.245	166 (32.10)	95 (32.44)	71 (31.64)	-1.727
Smoking Status: Current	N (%)	65 (12.08)	37 (12.05)	28 (12.12)	0.212	62 (11.99)	35 (12.14)	26 (11.78)	-1.097
Chemotherapy: Missing	N (%)	1 (0.19)		1 (0.43)	.				.
Chemotherapy: No	N (%)	132 (24.54)	41 (13.36)	91 (39.39)	61.852	119 (23.05)	65 (22.32)	53 (23.99)	3.956
Chemotherapy: Yes	N (%)	405 (75.28)	266 (86.64)	139 (60.17)	-62.800	400 (76.95)	229 (77.68)	171 (76.01)	-3.956
T-stage: 0/1	N (%)	362 (67.29)	196 (63.84)	166 (71.86)	17.231	340 (65.53)	195 (66.26)	145 (64.57)	-3.542
T-stage: 2/3	N (%)	176 (32.71)	111 (36.16)	65 (28.14)	-17.231	179 (34.47)	99 (33.74)	79 (35.43)	3.542
BMI category: Underweight/Normal <25	N (%)	141 (26.21)	64 (20.85)	77 (33.33)	28.377	130 (25.11)	73 (24.82)	57 (25.50)	1.574
BMI category: Overweight 25-<30	N (%)	152 (28.25)	81 (26.38)	71 (30.74)	9.645	150 (28.95)	85 (29.11)	64 (28.74)	-0.811
BMI category: Obesity I 30-<35	N (%)	130 (24.16)	89 (28.99)	41 (17.75)	-26.801	132 (25.57)	74 (25.32)	58 (25.89)	1.292
BMI category: Obesity II 35-<40	N (%)	73 (13.57)	45 (14.66)	28 (12.12)	-7.454	65 (12.64)	36 (12.48)	28 (12.85)	1.093
BMI category: Obesity III >40	N (%)	42 (7.81)	28 (9.12)	14 (6.06)	-11.573	40 (7.73)	24 (8.27)	15 (7.03)	-4.677
Margin Status: Missing	N (%)	7 (1.30)	6 (1.95)	1 (0.43)	-14.045				.
Margin Status: Close	N (%)	71 (13.20)	37 (12.05)	34 (14.72)	7.837	65 (12.65)	37 (12.63)	28 (12.69)	0.182
Margin Status: Negative	N (%)	451 (83.83)	261 (85.02)	190 (82.25)	-7.479	445 (85.76)	254 (86.31)	191 (85.03)	-3.643
Margin Status: Positive	N (%)	9 (1.67)	3 (0.98)	6 (2.60)	12.252	8 (1.59)	3 (1.06)	5 (2.28)	9.496
Tumor grade: Missing	N (%)	6 (1.12)	3 (0.98)	3 (1.30)	3.032				.
Tumor grade: 1	N (%)	16 (2.97)	5 (1.63)	11 (4.76)	17.886	15 (3.03)	8 (2.77)	7 (3.37)	3.440
Tumor grade: 2	N (%)	103 (19.14)	51 (16.61)	52 (22.51)	14.911	97 (18.74)	54 (18.45)	43 (19.12)	1.715
Tumor grade: 3	N (%)	413 (76.77)	248 (80.78)	165 (71.43)	-22.066	406 (78.23)	232 (78.78)	174 (77.51)	-3.057
Breast volume: Continuous	Mean (Median) [IQR[2]]	1130.72 (997.4) [684.40 - 1483.10]	1205.51 (1067.65) [702.10 - 1575.90]	1031.66 (906) [627.00 - 1359.30]	-27.570	1125.84 (1008.5) [657.20 - 1453.70]	1134 (1008.5) [674.50 - 1470.60]	1115.15 (1006.9) [627.00 - 1401.60]	-2.973

[†] D is the Standardized difference. Values of 10 or above suggest significant imbalance between fractionation groups.

[‡] IPTW is the Inverse Probability of Treatment Weighting.

[2]IQR is the Interquartile range, value for the 25th and 75th percentiles are reported.

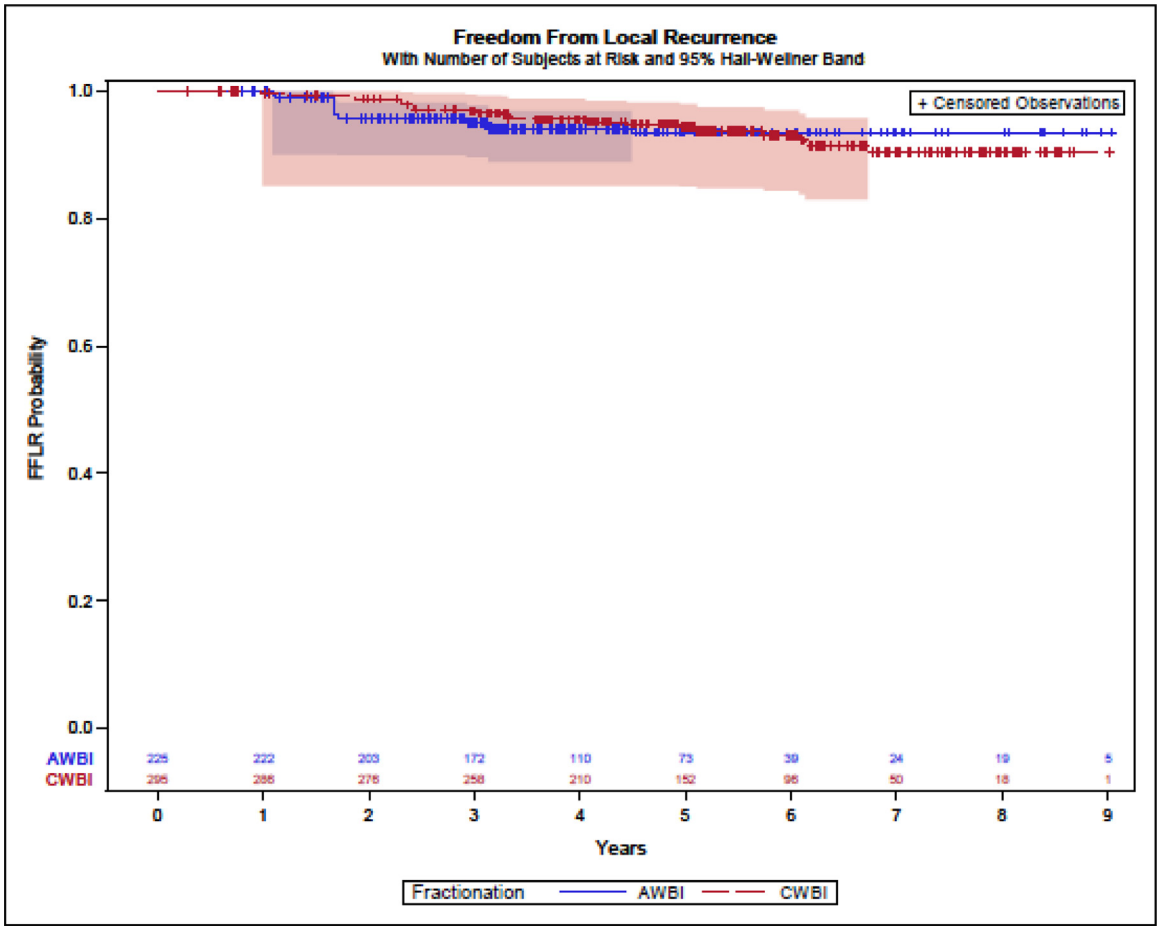

Fig. 1. Freedom from local recurrence—inverse probability of treatment weight adjusted.

majority of these cases received a boost (502 of 538 [93.3%]). The median patient age was 63 years (60 years among patients receiving conventional fractionation and 67 years among those receiving moderate hypofractionation). The characteristics of patients both before and after IPTW using the calculated propensity scores are shown in Table 1. The calculated propensity scores had sufficient overlap between the populations receiving moderate hypofractionation and conventional fractionation, and when converted into inverse probability weights for the treatment received, all patient weights were <3, suggesting no unduly influential cases for weighted analyses. Furthermore, it was observed from the weighted sample description that balance in the covariates was obtained through propensity weighting.

The overall study median follow-up time was 5.0 years (95% CI, 4.77-5.15 years), as calculated using the reverse censoring method of the product-limit OS estimate. The median follow-up time was 5.4 years (95% CI, 5.13-5.75 years) for conventional cases and 4.3 years (95% CI, 3.91-4.57 years) for hypofractionation cases.

The 5-year IPTW estimates for FFLR were 93.6% (95% CI, 87.8%-96.7%) in the moderate hypofractionation group and 94.4% (95% CI, 90.3%-96.8%) in the conventional fractionation group. The HR was 1.05 (95% CI, 0.51-2.17; $P = .89$) (Fig. 1).

The 5-year IPTW estimates for RFS were 87.8% (95% CI, 81.0%-92.4%) in the moderate hypofractionation group and 88.4% (95% CI, 83.2%-92.1%) in the conventional fractionation group. The hazard ratio was 1.02 (95% CI, 0.62-1.67; $P = .95$) (Fig. 2).

The 5-year IPTW estimates for OS were 96.6% (95% CI, 92.0%-98.5%) in the moderate hypofractionation group and 93.4% (95% CI, 88.7%-96.1%) in the conventional fractionation group. The HR was 0.65 (95% CI, 0.30-1.42; $P = .28$) (Fig. 3).

Of the 538 cases, 502 received a boost (301 of 307 in the conventional fractionation group and 201 of 231 in the moderate hypofractionation group). Only 1 patient who did not receive boost experienced a recurrence and only 2 died. The estimates of FFLR, RFS, and OS were almost identical to those in the entire sample when we conducted a sensitivity analysis restricted to the cases that received boost.

Discussion

Analysis of disease control outcomes in this large observational cohort of patients with triple-negative, node-negative breast cancer treated with whole-breast irradiation reveals no differences by dose fractionation. This adds meaningfully

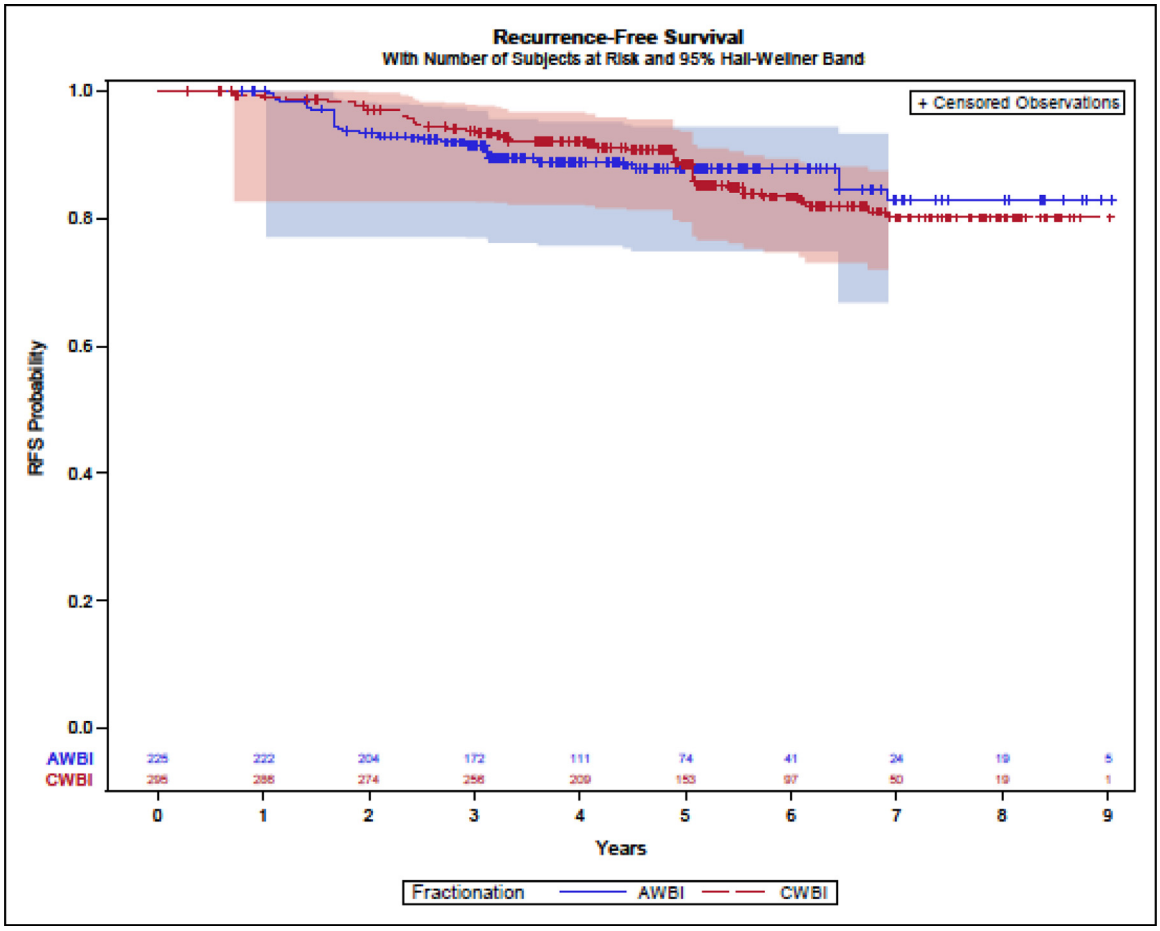

Fig. 2. Recurrence-free survival—inverse probability of treatment weight adjusted.

to the body of evidence supporting the use of moderate hypofractionation in patients with triple-negative disease.

Data now exist from several sources of information that, taken together, are reassuring on the important question of whether patients with triple-negative breast cancer are appropriate candidates for moderate hypofractionation. This includes 125 patients randomized to treatment with either conventional fractionation or moderate hypofractionation in a Canadian trial,[6] 77 patients randomized in a Chinese trial,[8] and 188 patients randomized in a trial from Denmark, Germany, and Norway (DBCG HYPO).[9] Specifically, in the OCOG trial, the hazard ratio comparing local recurrence outcomes of moderately hypofractionated to conventionally fractionated treatment in the 125 patients with triple-negative disease was slightly in favor of conventional fractionation at 1.27, but with a very wide 95% CI from 0.21 to 7.58.[6] In the Chinese trial, among 77 triple-negative patients, results were nearly identical in the 2 arms: 1 of 37 treated with moderately hypofractionated radiation therapy and 1 of 40 treated with conventionally fractionated radiation therapy had local recurrence (2 of 37 and 3 of 40 had locoregional recurrence).[8] In the DBCG HYPO Trial, among 188 patients who were ER and HER2 negative, 7 of the 98 patients treated with conventional fractionation and 2 of the 90 patients treated with hypofractionation had locoregional recurrence,[9] again not significantly different, and this time with the point estimate in the opposite direction from that in the OCOG analysis. Although none of these subgroup analyses within the randomized trials revealed a significant difference, given the small size of these subgroup analyses, concerns remained.

An Italian cohort study that included 48 triple-negative patients showed similar rates of relapse (21%) in patients treated with hypofractionation and those receiving conventionally fractionated radiation.[13] A larger Canadian cohort study of 603 patients also revealed no differences in outcomes with 10-year LRFS of 93.9% versus 92.2% for hypofractionation versus conventional fractionation (P = .47).[11] The current study's findings are consistent with these results and add substantially to the number of patients with triple-negative disease whose outcomes have now been compared, as advocated by leaders in the field—including both those who developed the most recent consensus guidelines in this area encouraging use of hypofractionation[3] and those who raised concerns about embracing hypofractionation too quickly.[10]

The primary limitation of this study is its observational design. Patients who received hypofractionation had more favorable disease characteristics and were less likely to receive chemotherapy. These imbalances would be expected to influence outcomes in opposite directions, with more favorable disease characteristics biasing estimates of disease

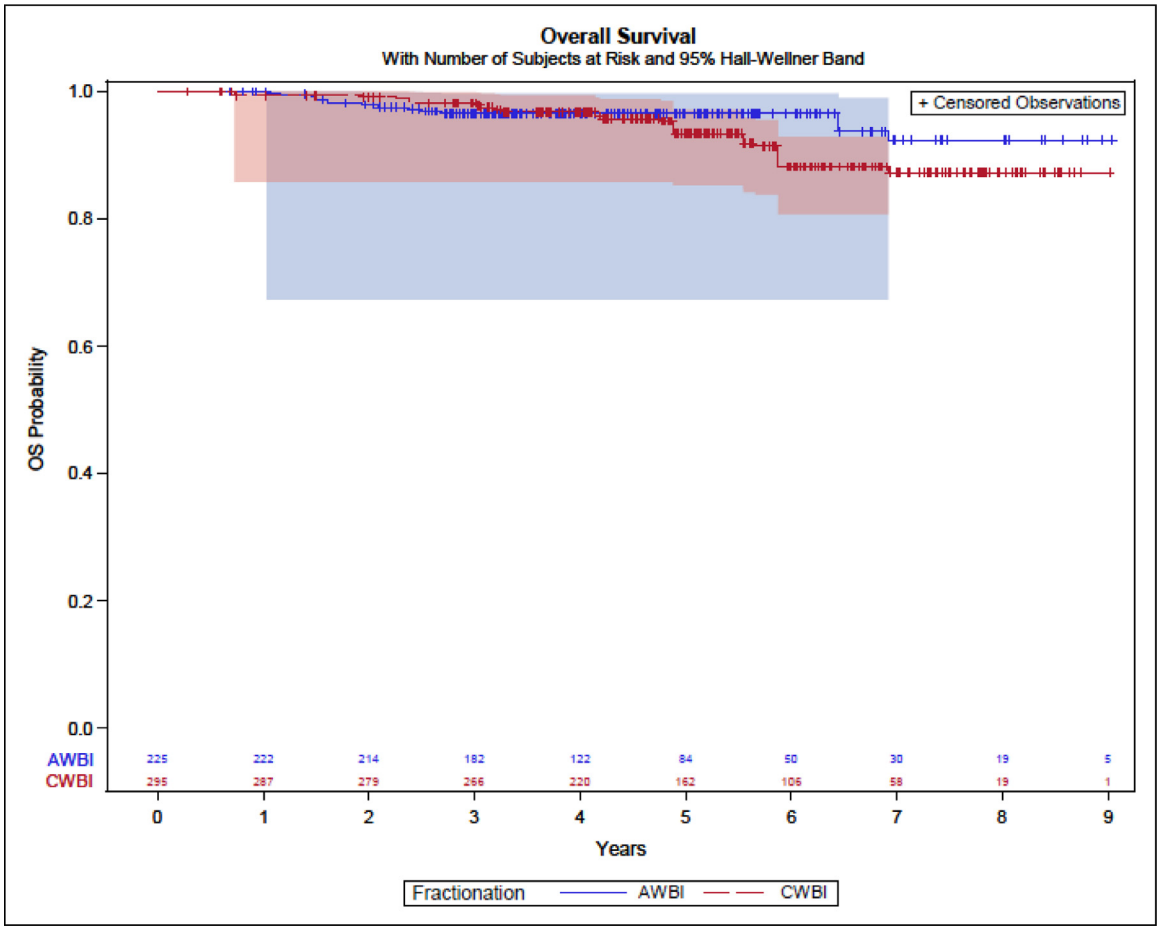

Fig. 3. Overall survival—inverse probability of treatment weight adjusted.

control upward in the hypofractionation group and lack of chemotherapy biasing estimates downward in that same group. Importantly, efforts were made to address confounding by these and other known prognostic covariates using appropriate statistical techniques. Patients treated with hypofractionation on the whole were treated slightly more recently than those treated with conventional fractionation, and the overall follow-up time was limited. Because triple-negative disease has lower rates of late recurrence than hormone receptor−positive disease, we believe that the 5-year results presented here are informative. We are also reassured by the consistency of the findings of this and the other 2 observational studies on this point with the findings of subgroup analyses from the randomized trials.

Conclusions

Hypofractionated radiation therapy in the adjuvant setting after breast-conserving surgery for breast cancer is clearly more convenient for patients, is less costly for both patients and society, and appears to have fewer acute[14] and late[2] toxicities[2] compared with conventionally fractionated regimens. Nevertheless, caution has been warranted when considering whether its application is equally effective for disease control in patients with the less common and more aggressive subtype of triple-negative disease,[10] which might conceivably have different fractionation sensitivity compared with more common hormone-sensitive subtypes and which has been shown to have a higher risk of local recurrence compared with other subtypes.[15] Taken together with other sources of information, this study provides evidence that supports the use of hypofractionated whole-breast irradiation in triple-negative patients, as in other subtypes.

References

1. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010;362:513–520.
2. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013;14:1086–1094.
3. Smith BD, Bellon JR, Blitzblau R, et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Pract Radiat Oncol* 2018;8:145–152.
4. Recht A, McArthur H, Solin LJ, Tendulkar R, Whitley A, Giuliano A. Contemporary guidelines in whole-breast irradiation: An alternative perspective. *Int J Radiat Oncol Biol Phys* 2019;104:567–573.

5. Thames Jr HD, Withers HR, Peters LJ, Fletcher GH. Changes in early and late radiation responses with altered dose fractionation: Implications for dose-survival relationships. *Int J Radiat Oncol Biol Phys* 1982;8:219–226.
6. Bane AL, Whelan TJ, Pond GR, et al. Tumor factors predictive of response to hypofractionated radiotherapy in a randomized trial following breast conserving therapy. *Ann Oncol* 2014;25:992–998.
7. Smith BD, Bentzen SM, Correa CR, et al. Fractionation for whole breast irradiation: An American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011;81:59–68.
8. Wang SL, Fang H, Hu C, et al. Hypofractionated versus conventional fractionated radiotherapy after breast-conserving surgery in the modern treatment era: A multicenter, randomized controlled trial from China. *J Clin Oncol* 2020;38:3604–3614.
9. Offersen BV, Alsner J, Nielsen HM, et al. Hypofractionated versus standard fractionated radiotherapy in patients with early breast cancer or ductal carcinoma in situ in a randomized phase III trial: The DBCG HYPO trial. *J Clin Oncol* 2020;38:3615–3625.
10. Recht A. Hypofractionated whole-breast irradiation: Case closed? *J Clin Oncol* 2020;38:3584–3586.
11. Lalani N, Voduc KD, Jimenez RB, et al. Breast cancer molecular subtype as a predictor of radiation therapy fractionation sensitivity. *Int J Radiat Oncol Biol Phys* 2021;109:281–287.
12. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015;34:3661–3679.
13. Lazzari G, Terlizzi A, Leo MG, Silvano G. Tumor grade and molecular subtypes on local control in breast cancer radiotherapy: Does fractionation really matter? A retrospective control study group. *Clin Transl Radiat Oncol* 2018;15:7–12.
14. Shaitelman SF, Schlembach PJ, Arzu I, et al. Acute and short-term toxic effects of conventionally fractionated vs hypofractionated whole-breast irradiation: A randomized clinical trial. *JAMA Oncol* 2015;1:931–941.
15. Arvold ND, Taghian AG, Niemierko A, et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. *J Clin Oncol* 2011;29:3885–3891.